PATENT SPECIFICATION

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(54) DRESSINGS FOR USE ON A MAMMALIAN BODY AND CAPABLE OF FORMING A GALVANIC COUPLE THEREWITH

I, MAURICE SEIDERMAN, a citizen of the United States of America of 3306 Deronda Drive, Hollywood, California 90068, United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The present invention relates to dressings for use on a wound or lesion on a

mammalian body and capable of forming a galvanic couple therewith.

The need to provide protection for a wound, lesion or the like on an animal body during the healing thereof has long been recognized. Bandages, surgical dressings and coatings are often used for this purpose. More recently, surgical grafting techniques have been developed to avoid the oxygen impermeability problems encountered with extensive use of bandage-like protective coatings. Although skin grafting is quite successful when the patient's own skin is used, grafts from donors often give rise to rejection problems preventing the proper therapeutic effects. Thus, other proteinaceous materials such as collagen have been employed in oxygen-permeable protective materials.

In recognition of the highly favorable, inherent characteristics of collagen which render it adaptable for providing protective films for wounds, lesions and the like, I have developed a process for the formation of adherent films disclosed in my U.S. Patent Specification No. 3,563,228 issued February 16, 1971. Briefly described, that earlier patent relates to the application of an electric field, of 20 suitable polarity, to a dispersion of undenatured collagen fibrils to cause

electrochemical-linking between the fibrils of the dispersion. The collagen, thus applied, is also capable of linking to native collagen fibrils exposed at the wound site to effect a highly adherent protective surface thereover.

In recognizing the advance over the prior art provided by my U.S. Patent Specification No. 3,563,228, it would be desirable to provide these adherent, skin-like protective coatings but without the need for application of an external power source to provide the iontophoretic impetus therefor, it being appreciated that the electric apparatus are often bulky and, oftentimes require the patient to be treated at some central location. Accordingly, it is desirable to be able to provide these protective coatings by continuous treatment of the patient without significant

restrictions upon ambulation or the necessity of confinement.

Further along these lines, the utility of an electric field in medical treatment is, of course well known. For example, it has been commonplace to provide bandage-35 like articles with electrodes comprising dissimilar metallic materials to create a galvanic cell for various types of clinical treatment. These articles, conventionally termed voltaic plasters, have been devised for the iontopheric administration of certain medicaments through a patient's skin. Note, for example, United States Patent Specification Nos. 116,562, No. 175,974, No. 222,276, No. 393,741 and No. 40 1,967,927.

The prior art voltaic plasters suffer numerous significant disadvantages, however. Perhaps the most important are the tendencies towards metal poisoning and/or for electrode burns due to the materials employed, chiefly based upon

copper and zinc as the dissimilar materials for the galvanic cell. Currently, when it is desired to iontophoretically administer topical medicaments, external power sources are employed. Note, e.g. United States

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	Patent Specification No. 3,163,166, as well as my earlier United States Patent Specification No. 3,563,228.	
	Moreover, all prior art methods based upon the application of an electric field	
	to the body have hitherto employed substantial voltages and/or currents which not	
5	only tend to be discomforting to the patient, but can actually traumatize the area	5
	proximate the point of application.	
	Consequently, it is most desirable to provide a therapeutic iontopheric	
	treatment of mammalian bodies which optimizes the healing effect thereof while	
10	minimizing the highly deleterious side effects and eliminating the need for bulky	10
10	external power sources. According to one feature of the present invention there is provided a dressing	10
	adapted for application to a mammalian body having a wound or lesion, the said	
	dressing comprising: (a) a dressing substrate adapted for application to the said	
	body; (b) a single metallic electrode; and (c) collagen and/or an ionizable or polar	
15	medicament in electrically co-operative relationship with the electrode: the face of	15
	the electrode remote from the said substrate being arranged such that in use at least	
	part thereof directly contacts the body, the said dressing being capable in use of	
	forming a galvanic couple between the said single electrode and the body when the	
20	dressing is applied over the wound or lesion and producing, without use of an external power source, a local current effective for iontophoresis whereby the	20
20	collagen or medicament is caused to contact or migrate within the wound or lesion.	LO
	According to one particular embodiment the dressing according to the present	
	invention may include a film-forming quantity of collagen fibrils whereby in use an	
	adherent skin-like protective membrane of the collagen fibrils electrochemically-	
25	linked to exposed collagen fibrils of the wound or lesion may be obtained. The	25
	collagen fibrils may, for example, be present in the form of a paste dispersion which	
	is desirably isotonic in character and optionally possesses selected metallic salts corresponding to those found in the animal body and present in similar minute	
	proportions to provide an electrolyte for the conduction of an electrical current.	
30	The collagen paste dispersion may if desired be impregnated in the substrate.	30
30	When such a collagen dispersion is disposed proximate to a wound or lesion on	
	the animal body to be treated, an electric field will be established between the	
	dispersion and the underlying area of tissue which exhibits a net effective negative	
	electrical characteristic.	25
35	Surprisingly, it has also been acertained that ionizable or polar medicaments	35
	may be effectively administered to a mammalian body using the dressing of the	
	invention to provide an iontophoretic impetus derived, in part, from the naturally- occurring local charges on the body to be treated in concert with the compatible	
	electrode of the dressing itself. If desired the dressing may include collagen as	
40	described above whereby a collagen film is formed at the same time as	40
	administration of medicament. The dressing according to the invention is	
	efficacious for the administration of any ionizable or polar medicament responsive	
	to an electric field; proteinaceous medicaments, or derivatives thereof, being	
4.5	preferred. The proteinaceous medicaments may be either undenatured or	45
45	denatured, e.g., the protein component of mild or strong silver protein and alginates. Additionally, there may be present various metallic salts or compounds,	43
	particularly when a denatured protein is employed. The most preferred metallic ion	
	is silver but other medicinally-effective metallic ions may be incorporated.	
	The dressing according to the invention employed to deliver the medicament	
50	to the mammalian body has an integral electrode of, e.g., foil in electrically-	50
	cooperative relationship with the medicament thereon. Aluminum is the most	
	preferred electrode material; however, the electrode may be fabricated from any of	
	a number of known metallic materials.	
	When the device, comprising the electrode and medicament, is applied to a	55
55	mammalian body, natural body fluids or, optionally, administrated isotonic or other electrolytic fluids, will establish the appropriate electric current and concomitant	33
	field for delivery of the medicament deep within the wound, lesion, or the like, on	
	the body. The medicaments envisioned for use in conjunction with this invention	
	comprise, but are not limited to, anti-infective, analgesic, bacteriostatic, and like	
60	ionizable or polar compounds, provided the compound is responsive, in terms of	60
	migration, to an electric field.	
	Fig. 1 is a bottom elevation view of a dressing according to an embodiment of	
	the massant invention, and	
	the present invention; and	
65	Fig. 2 is a side elevation view of the dressing of Fig. 1. In order to more fully illustrate the present invention, the following detailed	65

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description will be given in terms of a preferred embodiment and exemplified with respect thereto. The same is intended, however, to be illustrative and in no wise limitative Furthermore, as used in the context of the present invention, the term dressing

is meant to include all varieties of surgical dressings, regardless of physical configuration, which may be applied over a wound site to effect treatment therefor. Thus, the present invention envisions utility extending from the rather small adhesive bandages to large dressings of several square feet which may be applied to

burn victims.

The collagen dispersion for use in the dressing according to the invention may, for example, be prepared in the same manner as that described in U.S. Patent Specification No. 3,563,228, save for the fact that the collagen concentration in the instant dispersion is greater than the preferred 0.25% to 1% by weight concentration recited therein, e.g., up to about 50% by weight concentration, but most desirably having the consistency of soft table butter. More specifically, the instant collagen suspension may be prepared from bovine deep flexor tendon which has been cleaned and trimmed of fat and other extraneous matter, frozen, and subsequently sliced perpendicular to the longitudinal axis of the tendons to a suitable length of about 0.001 mm to 0.5 mm, preferably from 0.2 mm to 0.5 mm, albeit such a length is not critical. The collagen fibrils may then be disaggregated by treatment with proteolytic enzyme such as commercial ficin. This treatment may be achieved, for example, by gentle agitation for approximately 1 hour at 35°F in an aqueous solution of ficin. These fibrils are then washed with distilled water and treated with aqueous sodium chloride solution of approximately 1% by weight concentration for about 1 hour in two or three successive treatments (see U.S. Patent Specification No. 3,563,228). Having thus been prepared, these fibrils may then be added to a mixture of equal parts of ethanol and water, optionally containing approximately 0.2% cyanoacetic acid if long-term storage is anticipated; this mixture may then be agitated at a temperature approaching the freezing point thereof and subsequently homogenized by a conventional homogenizer. Optionally, the collagen dispersion may be produced according to the teachings of either U.S. Patent Specification No. 3,368,911 or the process of Battista as described in the Journal of Applied Polymer Science, 11, 41—498 (1967).

Such a dispersion of, for example, 10% by weight collagen concentration, will exhibit a paste-like or syrupy consistency, sometimes similar to that of soft butter. This paste or dispersion may then be enhanced for better conductivity by additions of saline (usually in amounts ranging from between 0.1% to 1.0% by weight), such as sodium chloride or potassium chloride or a mixture thereof, preferably in amounts to render the paste isotonic; that is, 0.9%. Metallic salts corresponding to those indigenous to the animal body may also be added in similar minute quantities, e.g. in amounts ranging between about 0.01% and 10% by weight. Selection of these salts, specifically to be rich in positive ions, is well within the purview of the skilled

artisan.

The most preferred embodiment in accordance with the present invention is illustrated in Figures 1 and 2. In Figure 1, there is shown a dressing generally designated as 40 bearing an area 42 which is a film of metallic material. Borne upon the film 42 is a film of collagen 44. The electrical potential is derived from a single active electrode, 42, which is in contact with the skin of the patient to be treated proximate the wound area. The electrode 42 is chosen to ensure it possesses negative electrical characteristics with respect to the collagen film, as shown in Figure 2.

The materials' selection for electrode 42 is restricted primarily upon considerations such as standard reduction potential to ensure the electrode maintains a negative potential with respect to the collagen film; the propensity for dissolution, to minimize the introduction of the electrode material within the wound area, as well as other considerations well known to the skilled artisan. Preferred electrode materials are, for example, aluminum, mild silver protein and zinc. However, when zinc is employed, due to its galvanic activity, it is preferable to form electrode 42 as a narrow strip adjacent collagen film 44, in contradistinction to the film shown in Figure 1, wherein the electrode is adjacent the entire periphery of collagen film 44.

Particularly beneficial results may be realized upon employing a mild silver protein film for electrode 42. Mild silver protein, a colloidal solution prepared by the interaction of protein and silver oxide and containing about 19 to 23% by weight silver, is a well known bacteriostatic agent. Only a small fraction of the fact, is somewhat demulcent. For a more comprehensive understanding of the uses and effects of mild silver protein, see Goodman and Gillman. The Pharmacological Basis of Therapeutics, 3rd Edition, McMillan, 1969.

The mild silver protein membrane may be fabricated to exhibit either a propensity to disintegrate in moisture or, with good wet strength to preclude such occurrence. Accordingly, the electrode material itself may take an active role in the healing process.

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Another of the preferred electrode materials is aluminum, a relatively innocuous material with little tendency to dissolve when the dressing is employed. A dressing similar to that depicted in Figure 2 was fabricated for purposes of experimentation. The dressing 40 has an upper, liquid impervious layer 46 and conveniently possesses a pressure sensitive adhesive (not shown) on the obverse side in order to facilitate adherence of the dressing to the area for treatment. This test employed a conventional bandage commercially marketed under the trademark Curad. A thin foil of aluminum, for example, 0.002 to 0.003 inches thick. was adhered over a gauze area 50 of the bandage. A paste of collagen was prepared in accordance with the process described above and deposited over the electrode 42 by means of a doctor blade. The collagen membrane, 44, may be either supported or unsupported, and may be processed to yield the collagen dispersible or insoluble in water, as desired. Once the dressing was assembled as shown in Figure 2, a drop of saline solution was placed upon the collagen film. Potentiometric tests were performed upon the dressing at that time and indicated a voltage of 0.5 volts between the electrode and collagen film, and a current of 400 microamperes.

Other dressings were fabricated in similar fashion employing electrode materials as set forth in Table I. The voltage and current developed by each of these dressings is likewise set forth in Table I.

		TABLE I		
30	Electrode Material	Voltage (V)	Current (µa)	30
	Aluminum	0.5	400	. 30
	Zinc	1.2	200	
	Tin	0.5	50	
	Titanium	0.15	25	
35	Tantalum	0.1*	2.5	35

*reverse polarity

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It has been observed that the collagen dispersion borne upon the dressing substrate electrochemically-links in a very short amount of time under the influence of the electrical potential derived from the galvanic source. Moreover, the collagen film adherently and tenaciously attaches to the wound site through both mechanical and chemical linkages with the exposed, damaged collagen fibrils of the wound. Accordingly, it has further been observed that the dressing itself may be removed in a relatively short amount of time, leaving behind this highly adherent, skin-like collagen film. Moreover, it has been observed that the collagen film thus applied to the wound site, upon limited dehydration, will contract somewhat and tend to close the wound in a natural manner. These, and other benefits, are realized upon application of materials totally acceptable to the animal undergoing treatment and, accordingly, rejection is rare.

Moreover, various modifications may be made to the collagen-containing dressing of the present invention. For example, mild silver protein may be mixed with the collagen dispersion to form a paste of enhanced electrochemical activity. Further, the conductivity of mild silver protein has been found to be enhanced by a fine spray or mist of ammonia prior to use. Thus, the relative electrical potential between the electrode and the collagen film is capable of a wide range of selection in order that the dressing be adapted for tailor-made operation. This is particularly true as the electrochemical-linking phenomenon is a strong function of electrical potential and may be advanced or retarded based upon materials selection.

It has also been determined that the notable benefits of practicing the present invention may be realized by impregnating either the substrate itself or simple tissue paper with the appropriate collagen dispersion, with or without additions, rather than depositing the collagen upon a conventional dressing substrate. The impregnated paper, whether readily disintegratable or possessing wet strength, may

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	then be utilized in the dressing of the invention. In like vein, the collagen dispersion, with or without additions, may be dried to a film, supported or unsupported, and used without need of a separate substrate. These embodiments may prove highly beneficial for treatment of extensive wound areas such as, for	
5	example, burns. Also, the collagen film may be electrically linked prior to its application to the wound area. Thus, the pre-linked film or membrane may be placed over the area to be treated and the dressing of the invention then applied to effect linking between	5
10	the collagen membrane and damaged collagen fibrils of the wound. It is observed that prior art voltaic plasters suffer numerous disadvantages, the most significant being risk of metal poisoning and/or electrode burns to the body being treated due to the construction of the bandage from highly active dissimilar metals as the galvanic electrode materials, and an inability to effectively deliver a	10
15	wide range of medicinally effective medicaments. Both of these significant drawbacks may be reduced or avoided by the present invention, which provides in one embodiment an integral electrode on a bandage substrate having a quantity of medicament also borne thereon. When applied to a mammalian body, natural body fluids or applied isotonic fluids will create a voltaic effect whereby the medicament is caused to migrate deeply within the wound or lesion, to elicit its desired	15
20	pharmacologic response. In part, the improvement derived from the present invention is coupled with the recognition that a mammalian body possesses a slight, inherent negative electric charge, particularly at areas proximate the site of the wound or lesion. Thus by appropriate design of a delivery device, materials may be employed which	20
25	advantageously utilize this electrical characteristic thereby overcoming the need for dissimilar electrodes to effect the galvanic cell while yet providing for the generation of a suitable electric field for the iontophoretic impetus. The improvement in the iontophoretic administration of medicaments using a dressing of the present invention lies also, in part, in administering a broad range of	25
30	while numerous anionic, cationic, and polar medicaments, including certain amphoteric medicaments, are envisioned within the scope of the present invention, the preferred are proteinaceous medicaments, either undenatured or denatured. Thus these preferred medicaments include for example, the protein component of	30
35	mild or strong silver protein, and alginates. Additionally, various effective metallic salts may be employed in this iontophoretic administration method in conjunction with the protein or derivative thereof. It has been determined that the proteinaceous medicament may be employed alone when the protein component is not denatured. When however, that protein component is denatured, it is	35
40 '	particularly beneficial to employ a metallic salt, most preferably a silver salt. However, other medicinally-effective equivalent metallic salts might be utilized. Likewise, other medicaments including, particularly, Dexamethasone Sodium Phosphate, Methylprednisolone Sodium Succinate, Flurandrenolide, and Amphotericin are preferred compounds for use in conjunction with the present	40
45	invention. These compounds may be employed individually or in admixture, with or without the additional presence of metallic salts, or denatured or undenatured mild silver proteins. Moreover, for example various steroids, antibiotics and antifungal compounds may also be employed, together or separately as might be desired. Further medicinally-effective compounds and preparations may be	45
50	selected from specific pharmacological effects, such selection being within the scope of those skilled in the art. The most preferred proteinaceous medicament is the antiseptically-effective mild silver protein, which is a colloid of silver with protein, containing on the order of about 10 to 25% by weight silver. This material is readily available,	50
55	commercially; and is described in "The Merck Index", Merck & Co., Inc., 5th Edition, 1940, page 458. However, other anti-infectious, analgesic and bacteriostatic proteinaceous compounds may, for example, be employed to this end. In electrically-cooperative relationship with the medicament is an electrode,	55
60	which may assume any of a number of physical configurations. Most preferably it is a metallic foil, although any suitable metallic material may be utilized and may be deposited in the form of a liquid such as, for example, dispersion, and subsequently dried. The electrode material should be selected from those known to be compatible with the mammalian body for the obvious reasons including e.g.	60
65	toxicity and irritation. As will become more apparent hereinbelow, a salient	65

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5	distinction between the dressing of the present invention and those of the prior art is the absence of a galvanic couple of active metallic components on the bandage substrate to which has been attributed the significant problems of electrode burns and/or metal poisoning indigenous to the latter. That is, the dressing of the present invention amplements in the present invention amplements.	
3	invention employs but a single metallic material for the electrode, regardless of the physical state or configuration thereof, i.e., a dressing such as illustrated in Figures 1 and 2. The most preferred electrode is a foil of aluminum metal. Other electrode	5
10	materials include, for example, copper, zinc, tin, and titanium, each of which will	
10 .	provide an effective positive charge with respect to the mammalian body. Should the medicament utilized require a net negative charge to provide the desired iontopheric impetus of proper polarity, such materials as tantalum might be utilized.	10
15	Regardless of the electrode material or configuration thereof, it is essential that the electrode be in electrically-cooperative relationship with the medicament	15
	to be iontophoretically administered. As a consequence, when the dressing is activated by electrolytic fluids such as, for example, body fluids or administered isotonic saline, voltaic interaction will establish an electric field between the	13
20	electrode and underlying wound site and generate a corresponding electric current, whereby the medicament is caused to migrate deeply within the wound in response thereto.	20
	The present invention envisions utility extending from small adhesive dressings to large dressing of several square feet which may be applied to, for example, burn	
25	victims. Exemplary of a particularly suitable dressing is that of Figure 1, denoted	
25	generally as 40, which comprises, e.g., a 6"×2" substrate 46, having a medial portion and terminal portions. The medial portion has adhered thereto a foil of, for example, aluminum metal, denoted as 42. The foil optimally comprises	25
	approximately one half of the total surface area of the dressing substrate; however, these dimensions are not critical provided the electrode material has sufficient	
30	surface area to provide the required iontophoretic-effective electric current. The central portion of the electrode 42 has coated thereon, or adhered thereto, a quantity of the desired medicament 44. Preferably, the medicament is	30
	applied as a paste or liquid to some absorbent material such as sterile tissue paper or sterile cloth or gauze. The medicament is allowed to dry and the porous carrier	
35	An optional embodiment employs a commercially-available surgical bandage.	35
	such as those marketed under the trademark "Curad". As opposed to the dressing of Figure 1, which may be made in relatively large dimensions, and wherein the	
40	terminal portions may or may not be coated with an adhesive substance, this alternate embodiment is designed for application to, for example, rather small cuts	40
	or abrasions. The dressing comprises a plastics or polymeric substrate having a medial portion and adhesively coated end portions with an absorbent gauze adhered to the substrate in the medial portion. Two foil electrodes are also borne	
45	upon the substrate and are caused to partially overlap the medial gauze area. The desired medicament may be applied to the gauze pad and allowed to dry.	45
	A dressing in accordance with this latter embodiment was prepared in order to ascertain the effectiveness of the iontophoretic administration of mild silver protein to a human body. The dressing employed is approximately 7.5 cm long and 2.5 cm	
50	wide. The gauze pad accounts for approximately 30% of the total surface area of the dressing and is coated with a solution of mild silver protein (LISP) made isotopic	50
	with 0.9% by weight sodium chloride. After the medicament has dried, two rectangular strips of aluminum foil having dimensions of about 2.5 cm×2.0 cm are	30
	adhered to the dressing substrate, partially overlapping the coated gauze area such that approximately 15% of each aluminum foil strip is in direct contact with the	
55	coated gauze pad.	55
	This dressing was placed on a human body over a minor wound. A drop of isotonic saline was administered to the coated gauze pad in order to establish voltaic action between the aluminum foil electrodes and the body. The electric	
60	potential was measured to be about 3/4 of a volt, and the current generated about 10 microamperes. In response to the electric field thus generated, the silver protein medicament migrated deeply within the wound at a rate much greater than were the electric field absent.	60
	A similar dressing was prepared employing as a substrate, a commercially-	
65	available bandage, marketed under the name "Air-Vent Tape Clear", by Johnson & Johnson. This bandage, measuring about 9.0 cm×2.6 cm, was placed with the	65

the body to establish an iontophoretically-effective electric current between the medicament and the body to cause migration of the medicament into the wound or

lesion thereon.

5	11. A dressing as claimed in any one of claims 1 to 9 wherein the substrate comprises a medial portion bounded by terminal portions, ionizable or polar medicament being borne upon the substrate within the medial portion, the electrode being borne on at least one of the terminal portions and partially overlapping the medial portion in electrically-cooperative relationship with the medicament.	5
10	12. A dressing as claimed in any one of the preceding claims wherein the medicament is absorbed within a carrier selected from sterile paper, sterile cloth and hydrogel polymers, the said carrier being adhered to the dressing. 13. A dressing as claimed in claim 1 further including an electrochemically-effective quantity of an electrolyte. 14. A dressing as claimed in claim 13 wherein the electrolyte is sodium	10
15	chloride, potassium chloride or a mixture thereof. 15. A dressing as claimed in any one of claims 1 to 3, 13 and 14 including a film-forming quantity of collagen fibrils so as to obtain in use an adherent skin-like protective membrane of the collagen fibrils electrochemically-linked to exposed collagen fibrils of the wound or lesion.	15
20	16. A dressing as claimed in claim 15 wherein the collagen fibrils are present in the form of a paste dispersion supported by the substrate and containing an electrolyte. 17. A dressing as claimed in claim 16 wherein the collagen dispersion is coated on the substrate.	20
25	18. A dressing as claimed in claim 16 wherein the collagen dispersion is impregnated in the substrate. 19. A dressing as claimed in any one of claims 16 to 18 wherein the collagen dispersion is dried. 20. A dressing as claimed in claim 15 wherein the metallic electrode is in the	25
30	form of a metallic film upon which the collagen fibrils are borne in electrically co- operative relationship such that, in use, upon introduction of fluid to the dressing, a galvanic current is generated whereby the collagen fibrils electrochemically link to form the adherent, skin-like protective membrane. 21. A dressing as claimed in claim 20 further including mild silver protein	30
35	mixed with the collagen fibrils. 22. A dressing as claimed in claim 20 wherein the metallic electrode is mild silver protein. 23. A dressing as claimed in claim 1 substantially as herein described. 24. A dressing as claimed in claim 1 substantially as herein described with reference to the drawings.	35

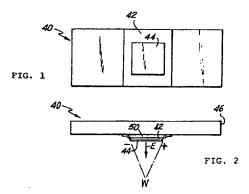
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COMPLETE SPECIFICATION

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